K063868

510(k) SUMMARY

Date of Summary: December 28, 2006

MAY 25 2007

Product Name
Waters MassTrak™ Immunosuppressants Kit

Sponsor
Waters Corporation
34 Maple Street
Milford, MA 01757

Manufacturer
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Substantially Equivalent Devices
The MassTrak Immunosuppressants Kit is substantially equivalent to the Dade Behring Emit® 2000 Tacrolimus Assay and Calibrators and the Microgenics CEDIA® Tacrolimus Assay and Calibrators in its intended use and for the quantitative determination of Tacrolimus concentration in human whole blood as an aid in the management of kidney and liver transplant patients receiving therapy with Tacrolimus.

ITEM	DEVICE	PREDICATE I	PREDICATE II
Intended Use	The Waters MassTrak™ Immunosuppressants Kit is indicated for the quantification of the immunosuppressive drug Tacrolimus (FK506; Prograf) in liver and kidney transplant patient whole blood samples for the purposes of monitoring drug levels to direct subsequent patient dosing.	Intended for *in vitro* quantitative analysis of Tacrolimus and metabolite in human whole blood as an aid in the management of Tacrolimus therapy in liver and kidney transplant patients. The Emit® 2000 Tacrolimus Calibrators are intended for use as a reference in measuring Tacrolimus in human whole blood using the	Intended for the quantitative determination of Tacrolimus in human whole blood using automated clinical chemistry analyzers as an aid in the management of kidney and liver transplant recipients receiving Tacrolimus therapy. CEDIA® Tacrolimus Calibrators are intended for calibration of the CEDIA® Tacrolimus Assay in whole blood.

ITEM	DEVICE	PREDICATE I	PREDICATE II
	Waters MassTrak™ Immunosuppressants Kit	Emit® 2000 Tacrolimus Assay Emit® 2000 Tacrolimus Calibrators	CEDIA® Tacrolimus Assay CEDIA® Tacrolimus Calibrators
		Emit® 2000 Tacrolimus Assay.	
Analyte	Tacrolimus	Tacrolimus	Tacrolimus
Matrix	Whole blood	Whole blood	Whole blood
Assay range	3-30 ng/mL	2-30 ng/mL	2-30 ng/mL
Analytical specificity	Liquid chromatography / tandem mass spectrometry (LC/MS/MS)	EMIT (Enzyme Multiplied Immunoassay Technology)	Clinical Chemistry Analyzer
Calibrator	Six (6) levels (0 ng/mL 3 ng/mL, 6 ng/mL, 12 ng/mL, 20 ng/mL, and 30 ng/mL of Tacrolimus)	Six (6) levels (0 ng/mL 2.5 ng/mL, 5 ng/mL, 10 ng/mL, 20 ng/mL, and 30 ng/mL of Tacrolimus)	Two (2) levels (0 and 30ng/mL)
Storage	Kit is stored at -20°C Reconstituted calibrators and QCs are stored at 2°C to 8°C	Reagents are stored at 2°C to 8°C	Reagents are stored at 2°C to 8°C Calibrators are stored at -20°C
Stability	Kit stable for up to 2 years from manufacture date when stored as indicated above	Reagents stable for up to 18 months from manufacture date when stored as indicated above	Reagents and Calibrators stable for up to 24 months from manufacture date when stored as indicated above

Product Description

The MassTrak Immunosuppressants Kit for Tacrolimus is an *in vitro* medical device intended to facilitate quantitative determination of Tacrolimus in human whole blood as an aid in the management of kidney and liver transplant patients receiving Tacrolimus drug therapy.

Tacrolimus (FK506) is an immunosuppressive agent approved by FDA that has been successfully implemented following the transplantation of kidney and liver organs. Monitoring and maintenance of appropriate blood levels of Tacrolimus is important to prevent rejection, infection, and other adverse events. Analytical methodology using a high-performance liquid chromatography (HPLC) apparatus equipped with a tandem mass spectrometer detector (LC/MS/MS) is considered to be a candidate reference method for Tacrolimus quantification. Sample preparation is based on simple protein precipitation and centrifugation to isolate the supernatant that is suitable for analysis by LC/MS/MS.

The components of the kit are intended for use with an LC/MS/MS system. The kit

materials – calibrators, quality control materials, internal standards, and neat solutions, as well as a MassTrak™ 2.1 x 10 mm C18 cartridge column - have been optimized for use with the Waters Quattro micro and Alliance 2795 System, but can be used with any LC/MS/MS configuration optimized for quantification. System calibration is performed using the kit calibrators, and analysis is completed with the aid of the internal standard, ascomycin. The neat solution is used only for tuning the mass spectrometer. The HPLC cartridge columns was selected to isolate Tacrolimus from compounds extracted from the sample that may lead to ion suppression.

Intended Use

The Waters MassTrak Immunosuppressants Kit is indicated for the quantification of the immunosuppressive drug Tacrolimus (FK506; Prograf) in liver and kidney transplant patient whole blood samples for the purposes of monitoring drug levels to direct subsequent patient dosing.

Summary of Technology

Sample preparation is based on simple protein precipitation. Whole-blood samples are treated with an organic solvent to precipitate the protein and extract the compound of interest into the organic phase. The supernatant from a protein-precipitated whole-blood sample is injected into an on-line, solid phase, extraction device to perform a preliminary clean-up of the prepared sample. The internal standard and analyte of interest are then eluted into the ionization source of the tandem mass spectrometer.

The first stage of mass spectrometry selects precursor ions from the ion source according to their mass-to-charge ratios (*m/z*). Ions whose *m/z* ratios correspond to that of the analyte of interest are passed to a collision cell where they collide with a neutral gas, generating structurally specific product ions. The second stage of mass spectrometry passes ions corresponding to one of these product ions (usually the most abundant) to the detector. Therefore, interferences with the signal generated by the analyte of interest will be seen only if the interfering chemical entity generates precursor and product ions of the same *m/z* values (that is, structural isomers).

The assay method requires the user to tune the instrument in the presence of ammonium acetate. Ammonium adducts are created which are then measured by the mass spectrometer. The most prominent product ion (*m/z* 768) of the ammonium adduct of Tacrolimus (*m/z* 821) is detected using tandem mass spectrometry. The measured response of Tacrolimus is compared to the measured response of the internal standard.

The quantification of Tacrolimus in whole blood extracts is made against a linear standard curve prepared using reconstituted freeze-dried whole blood matrix calibrators (6 levels, with targets varying by lot number). The analysis is controlled using three levels of reconstituted freeze-dried whole blood matrix quality control materials (with targets varying by lot number).

Performance Data

All performance data for the MassTrak Immunosuppressants Kit were gathered at the clinical sites using Alliance HT 2795 High Performance Liquid Chromatography Systems

coupled to Quattro micro triple quadrupole mass spectrometers. Data and results are presented in Section 20: Design Testing Summary Report of the 510(k) submission.

1. Analytical Performance:
   a. Precision/Reproducibility
      Precision studies were conducted by assaying three levels of spiked whole blood pools according to CLSI EP5-A2. The pools were prepared from EDTA drug free whole blood with Tacrolimus spiked at three analytical levels: Low, Medium and High. Specimens at each level were analyzed in duplicate twice per day for 20 days. For within-run precision and total precision, a coefficient of variation (%CV) $\leq$ 10% is deemed acceptable.

   b. Linearity/assay reportable range
      Linearity was assessed according to CLSI EP6-A using nine test samples. The test samples were prepared by mixing patient specimens with low and high Tacrolimus concentrations in defined proportions such that the final Tacrolimus concentrations were known relative to each other. Replicate determinations of each test sample were made. Second order and third order polynomial curves are fitted to the data and the assay is deemed to be linear if the coefficients for the second order and third order terms are not significantly different from zero at the 95% confidence level.

   c. Patient Sample Stability
      Patient samples were analyzed in replicate before and after storage under defined conditions to determine the effect of those conditions on the Tacrolimus concentration measured by the device. A freeze-thaw study (three cycles) was also conducted. Conditions that did not cause a statistically significant change from the initial Tacrolimus concentration (*t*-test, $p \geq 0.05$) or caused a change of $\leq$ 10% from the initial Tacrolimus concentration were acceptable.

   d. Sample Dilution
      A minimum of ten patient samples with Tacrolimus concentrations > 15ng/mL were analyzed before and after 1:1 dilution with drug-free whole blood and 1:1 dilution with MassTrak Immunosuppressants Kit Calibrator 1. The results were considered acceptable if, for each sample, the Tacrolimus concentration measured for the undiluted sample and the Tacrolimus concentration calculated from the sample diluted 1:1 with drug-free whole blood or MassTrak Immunosuppressants Kit Calibrator 1 varied by $\leq$ 10% of the initial concentration.

   e. Spike & Recovery
      The recovery performance of the device was assessed using patient samples supplemented with 5, 10 or 20 ng/mL Tacrolimus and using drug-free whole blood spiked with Tacrolimus from 0.5 – 30 ng/mL to ensure that the analytical range of the assay was covered. Triplicate determinations of each sample were made and recovery is considered acceptable if the overall

mean recovery for each concentration is in the range 90% - 110%.

f. Interference Studies
Potential interferences were evaluated according to CLSI EP7-A and with reference to the list of potential interfering substances in the FDA Class II Special Controls Document and in the FDA Guidance for Industry Bioanalytical Method Validation Document. Known amounts of exogenous or endogenous materials were spiked into separate aliquots of a base pool of drug-free whole blood that had been supplemented with Tacrolimus at a concentration of approximately 20 ng/mL. To test the effect of anticoagulants at up to 5x the normal concentration and to test the effect of hematocrit 15% to 60%, drug-free whole blood was first adjusted to simulate the appropriate condition before spiking with Tacrolimus to a concentration of approximately 20 ng/mL. In all cases, sufficient replicate determinations were made to ensure 95% confidence and 95% power. Any interference that causes a change in measured Tacrolimus concentration of > 10% is considered to have a significant effect and must be investigated further to determine the maximum concentration at which no interference is observed.

g. Accuracy
The accuracy of the measurements performed using the MassTrak Immunosuppressants Kits was established by measuring the Tacrolimus concentrations in a series of 44 samples provided by the Tacrolimus International Proficiency Testing Scheme (www.bioanalytics.co.uk). The results for all samples were considered acceptable by the Scheme (±3 SD of method mean).

2. Comparison Studies
a. Method Comparison
Method comparison studies were conducted according to CLSI EP9-A2 to compare the results obtained with the MassTrak Immunosuppressants Kit (the "Test Method") with those obtained using the test laboratory's current methodology (the "Comparative Method"). According to the FDA Special Controls Document, a minimum of 50 samples for each transplant type were compared at each site. Duplicate analyses of each patient sample were performed in each of two Test Method assays and two Comparative Method assays, with all four assays performed on the same day. A maximum of 10 patient samples were compared in one day. The predicted bias at the lower (5 ng/mL) and upper (15 ng/mL) limits of the therapeutic range for Tacrolimus (Lake Louise Consensus Conference on Tacrolimus monitoring, Oellerich et al, 1998) are calculated using Deming Regression analysis as described in EP9-A2 and the results of the Test Method for each tissue type are considered acceptable if the bias at both concentrations is ≤ 10% .

In addition, the Tacrolimus concentrations for a series of International Proficiency Testing Samples (http://www.bioanalytics.co.uk/html/

tacrolimus_scheme.html) were determined using the MassTrak™ Immunosuppressants Kit and the results compared to those reported to the Scheme for the same samples analyzed using the EMIT 2000 Tacrolimus device.

Statement of Safety and Efficacy

The information provided in this pre-market notification demonstrates that the MassTrak Immunosuppressants Kit is substantially equivalent to the currently-marketed CEDIA® Tacrolimus Assay and Emit® 2000 Tacrolimus Assay.

Waters Corporation has presented laboratory testing in this pre-market notification. Data and results were collected and prepared in accordance with the established guideline, "Class II Special Controls Guidance Document: Cyclosporine and Tacrolimus Assays; Guidance for Industry and FDA" September 16, 2002.

The information presented provides assurance that the MassTrak Immunosuppressants Kit will meet the requirements that are considered acceptable for its intended use.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAY 25 2007

Waters Corporation
c/o Ms. Fran White
MDC Associates, LLC
163 Cabot Street
Beverly, MA 01915

Re: k063868
Trade/Device Name: MassTrak™ Immunosuppressants Kit
Regulation Number: 21 CFR 862.1678
Regulation Name: Tacrolimus test system
Regulatory Class: Class II
Product Code: MLM, JIT, JJX
Dated: May 18, 2007
Received: May 21, 2007

Dear Ms. White:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (240) 276-0490. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address at http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Jean M. Cooper, M.S., D.V.M.

Jean M. Cooper, M.S., D.V.M.
Director
Division of Chemistry and Toxicology
Office of *In Vitro* Diagnostic Device
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Enclosure

Indications for Use

510(k) Number (if known): K063869

Device Name: Waters MassTrak™ Immunosuppressants Kit

Indications For Use:

The Waters MassTrak Immunosuppressants Kit is indicated for the quantification of the immunosuppressive drug Tacrolimus (FK506; Prograf) in liver and kidney transplant patient whole blood samples as an aid in the management of tacrolimus therapy.

Prescription Use XXX AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device Evaluation and Safety
510(k) K063869